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The Association between Knee Osteoarthritis Progression and Diabetes Mellitus: A Systematic Review and Meta-Analysis

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Abstract

Background: Diabetes mellitus (DM) and osteoarthritis (OA) are commonly increased in prevalence and commonly occur together, both of them are leading causes of disability. The relationship between Diabetes mellitus (DM) and osteoarthritis (OA) is not known, consequently, the purpose of this study to identify if there is an association between them.

Aim of Study: To investigate the association between diabetes mellitus and knee osteoarthritis and the effect of diabetic type or diabetic duration on the progression of knee osteoarthritis through a systematic review.

Material and Methods: Systematic searches were done on the following electronic databases MEDLINE / PubMed, Cochrane Library ,Web search, SAGE, Google scholar, Scopus, since the inception of these databases From February 2022-February 2023.

Results: Fifty studies were included in the current review, 32 studies of them were included to identify the association between diabetes and knee OA, Ten studies were used to calculate the risk of knee osteoarthritis in diabetic patients, among 4148 patients, the overall OR was 1.24 (CI 1.14 to 1.35). Seven studies were used for the risk of DM in an OA versus non-OA subjects, among 2468 patients, the overall OR was 2.26 (1.28 to 4.01). The mean OA prevalence among diabetic patients was 34.29%, while DM prevalence among OA patients was 23.45%.

Conclusion: Diabetes mellitus is strongly associated with knee OA, and each of them is a major cause of others as seen by higher OA prevalence in diabetic patients and vice versa.

Key Words: *Knee osteoarthritis — Diabetes mellitus — Systematic review.*

Introduction

IN the US and around the world, the prevalence of diseases including diabetes mellitus (DM) and osteoarthritis (OA) is expected to rise **[1,2].** A growing body of research demonstrated that DM may negatively impact articular tissues and worsen OA, as well as the consequent rise in the coexistence of these two disorders.

The most common chronic joint condition and a major contributor to pain and disability worldwide is knee osteoarthritis **[3]. It** is a degenerative articular condition characterized by discomfort, mild to severe synovial inflammation, changed subchondral and peri-cartilaginous bone, and degraded articular cartilage. Damage to the cartilage is the last common endpoint in OA **[4].**

In healthy, asymptomatic, undamaged knees, the prevalence of magnetic resonance imaging **(MRI)** characteristics indicative of OA ranged from 4% to 14% in young adults to 19% to 43% in older adults aged 40 years *[5].* In addition to age, additional factors that affect prevalence rates include levels of physical activity and the type of **MRI** sequences used [6].

A metabolic disorder called diabetes mellitus is brought on by a breakdown in the body's system for processing glucose [4]. Although type 1 and type 2 diabetes inclinations vary, data on the incidence and prevalence of diabetes in children and adolescents have increased over the past few decades *[7].*

Type 1 diabetes (T1DM), which accounts for more than 90% of all instances of diabetes in children, is extremely prevalent in different nations, within countries, and among different ethnic populations **[8].** Over 387 million adults worldwide currently have type 2 diabetes (T2D), and by the year 2035, that number is expected to rise to 592 million [9].

The investigation of the relationship between the metabolic syndrome (MetS) and its related elements as potential risk factors for the onset and progression of OA has drawn greater attention in recent years. Studies have shown that inflammatory mediators released from adipose tissue may harm the

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metabolism of joints as well as other organs, despite the fact that the precise mechanism connecting both disorders is not yet fully understood **[10-12].**

Additionally, numerous efforts have been made to show a connection between persistent hyperglycemia and harm to the articular cartilage.

In fact, chondrocytes exposed to high levels of extracellular glucose may produce and deposit more advanced glycation end products (AGEs) and reactive oxygen species (ROS), which can cause inflammation and extracellular matrix damage **[13-15].** Through the activation of IL- lb and IL-12 among other cytokines, the disruption in glucose metabolism might affect the metabolism of chondrocytes and influence the development and progression of OA **[16].**

Material and Methods

This systematic review was reported in accordance with PRISMAprinciples & registered on PROSPERO (PROSPERO: CRD CRD42018081494) **[17].**

Information sources and search strategy:

Systematic searches were conducted on the following electronic databases EMBASE, MEDLINE / PubMed, Cochrane Library Web search, Scopus, SAGE, and Google Scholar including publications since the inception of these databases until February 2023.

Medical Subject Headings (MeSH) and free-text phrases were combined in the search technique, related to (association OR correlation OR link OR relation OR relationship) between (knee arthritis OR osteoarthritis OR arthrosis OR degenerative joint disease OR knee degenerative joint disease) and (diabetes mellitus, hyperglycemia, metabolic syndrome) OR the effect of diabetes on osteoarthritis (progression OR advance OR advancement).

Because this systematic review is regarded as an update of a previously published study and is being conducted in light of the publication as a significant new research with some modifications to the research questions as well as the inclusion and exclusion criteria, we searched the databases starting at their inception. We looked for pertinent publications in the reference lists of the included articles.

Eligibility criteria:

This review wasconsidering all studies that involve all ages, BMI male and female with or without primary knee osteoarthritis and diabetes mellitus (type 1 OR type 2). The patient had at least a grade 2 composite OA score, equivalent to grade 2 on Kellgren and Lawrence (KL) grade in at least one knee, and the patient with diabetes diagnosed by taking a blood sample or self-reported DM.

Studies were excluded if:

- Knee OA brought on by injuries and other problems.
- Systemic and connective tissue illnesses.
- Metabolic bone disease.
- Previous knee arthroscopy or surgery.
- Acute or persistent infection.
- Smoking, pregnancy, and cancer.
- Medicines used as corticosteroids.
- Scientific articles written in languages other than English.
- Poster presentations, editorials, letters, and conference proceedings.

Study selection:

Mendeley Desktop (version 1.17.11) was used to import all titles and abstracts, and it was from there that we eliminated duplicates and articles that didn't fit the inclusion criteria. Two reviewers (HA and KA) separately decided which papers met the preceding eligibility requirements as relevant. Both reviewers' lists were reviewed, and the full text of any papers they both identified was obtained. Consensus was used to resolve judgment differences. As a final arbiter, SF, a third reviewer, was used. Fig. (1) displays a flowchart of the study selection process. When necessary, we also got in contact with the main authors to ask for further information or data clarification.

Data extraction:

The required data was separately extracted by two reviewers (HA and KA). They compared their results to ensure that all pertinent data had been successfully extracted. The following items were extracted: Author and year of publication, title, type of study, research site, participant characteristics (diabetic group characteristics, OA and non-OA group characteristics) sample size, sex, age, weight, height, and body mass index), outcome (diagnosis of OA, knee OA severity), Exposure (diagnosis of diabetes, type of diabetes, associated metabolic disorder), outcome measure, result, authors conclusion.

Quality assessment:

Using the Newcastle-Ottawa Scale (NOS), a risk-of-bias evaluation measure for observational studies that is endorsed by the Cochrane Collaboration, two researchers (KA, HA) independently evaluated the quality of selected publications, The NOS is a tool commonly used in medicine as it is a validated instrument and with a long history of reliability. To avoid major disagreement between authors, 3 articles as pilot studies were assessed by 2 researchers (KA & HA) before starting the actual assessment. Discussion ensued until agreement was reached in order to resolve evaluation disagreements.

Eight components make up the NOS, which are divided into three categories: Comparison, outcome (cohort studies), and exposure (case-control studies), depending on the type of investigation. A number of response alternatives are offered for each issue. The highest quality studies are given a maximum of one star for each item, with the exception of the item linked to comparability, which allows the assignment of two stars. This star system is used to enable a semi-quantitative assessment of study quality. There are 0 to 9 stars in the NOS. Regardless of study quality, all studies were included in this review. Cohen's Kappa was used to determine how well the two reviewers agreed.

Statistical methods:

The prevalence of diabetes among OA patients and vice versa was calculated. 95% confidence intervals (CIs) and OR were taken into account as the effect sizes for all studies in this meta-analysis. The Cochran Q test and I^2 statistics were used to determine the degree of heterogeneity among the studies, with an I^2 between 50% and 90% potentially indicating significant heterogeneity **[20].**

We constructed random effects models using the inversed variance approach to pool the estimates from several studies due to the inter-study variability, and we then summarized the findings using forest plots. The link between diabetes and OA was expressed using odds ratios as the effect estimate. p-values less than 0 05 were used to show statistical significance.

By excluding one study at a time, sensitivity analyses were carried out, and a pooled estimate for the studies that remained were then computed. We intended to assess whether a single study significantly influenced the outcomes. RevMan, version 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, was used for the majority of analyses.

Results

Total of 933 references were presented in the search results of the chosen databases. A total of 831 references were checked for relevancy after duplicates were eliminated. After abstract assessment, 853 of these were eliminated because they didn't match the requirements for inclusion. More thorough analysis was done on the remaining 80 references' complete texts. Finally, 50 papers in total met the criteria for inclusion in our evaluation (Fig. 1). The two reviewers that examined the references agreed on 81% of the questions. 23 papers were used in the descriptive analysis, while 17 of the 50 studies contributed data for the meta-analysis.

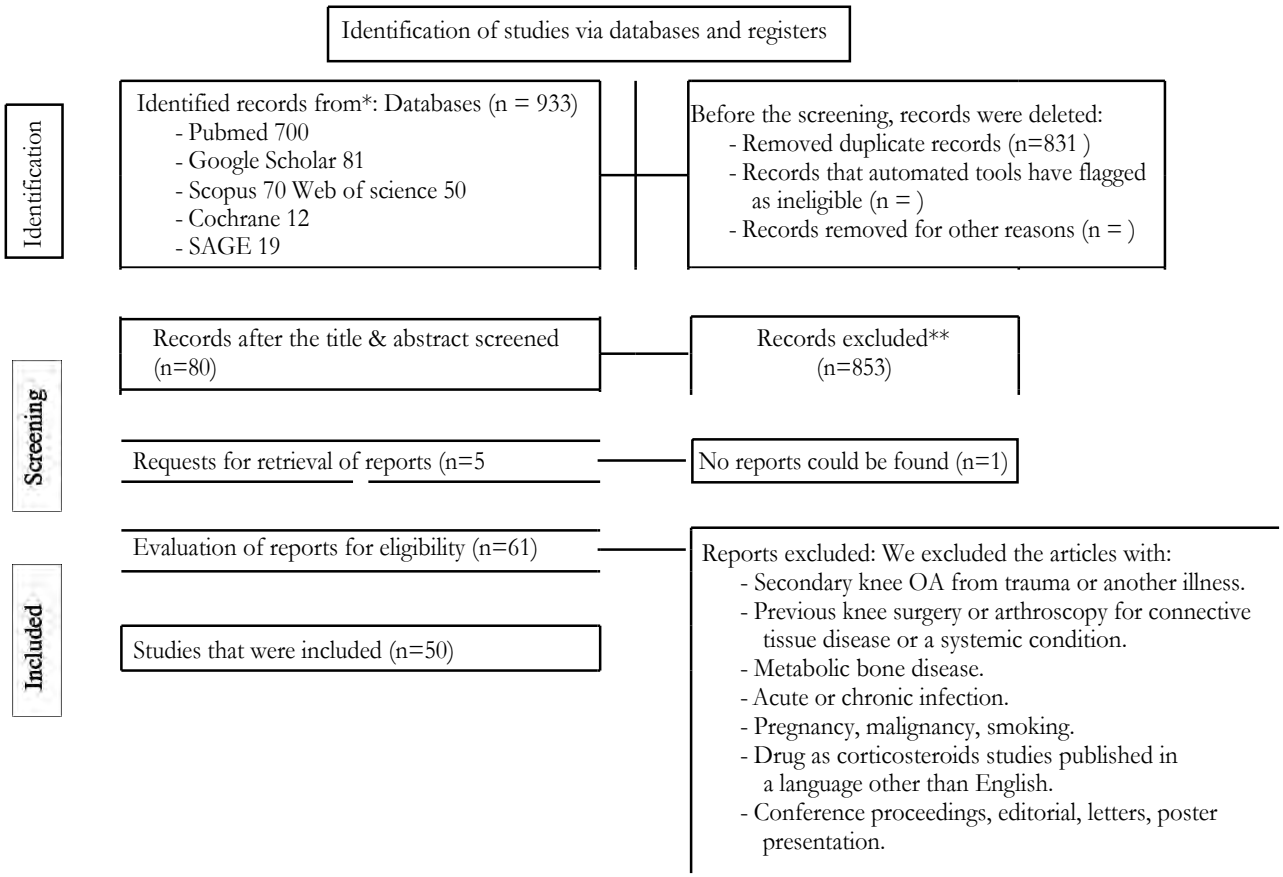

Fig. (1): Flow diagram.

Characteristics of included studies:

Eighteen studies of the 50 studies were cohort studies [21-38]; While eight case control studies [3,39-45], and twenty-four cross sectional studies [41-64]. Study characteristics showed in Table (1).

Quality assessment result:

Study quality was assessed using the Newcastle-Ottawa scoring system the majority of studies presented good quality. Thirty four studies took good quality [3,21-28,30-41,44,48,51,52,53,56,58,60-63, 65,68].

Fourteen studies have fair quality, not using an appropriate selection for sample [25,42,46,47, 49,50,54,55,57,59,64,66], outcome measure [25,46,48,64], and inappropriate comparability [46,54,55,57,67]. Two studies have poor quality [43,45].

Results from using the Newcastle Ottawa scale are shown in Table (1) seventeen cohort studies were graded of good quality and one study fair quality, while there were five case-control studies graded of good quality, one fair, and two poor-quality assessments. There were twelve cross-sectional studies graded as good quality and twelve studies graded as fair quality.

Prevalence of OA among patients with DM:

The prevalence was calculated by using the 13 studies of patients with DM, sex of them cohort studies [25,27,29,30,35]. Five of them were cross-sectional studies [46,47,50,53,57]. Two of them are case-control studies [41,69]. For 4403 patients with DM, the mean OA prevalence was 34.29%.

Prevalence ofDM among patients with OA:

The prevalence was calculated by using the 18 studies of patients with OA, three of them cohort studies, we used the baseline data [22,32,36]. Ten of them as cross-sectional studies [48,52,54,58,60-64,66]. Five of them are case-control studies [3,40,42,43,45]. For 12361 patients with OA, the DM prevalence was 23.45%.

Associations between OA and DM:

Fifty studies were included in the current review, forty-four of them were used to determine the association between OA & DM, and six studies did not have baseline data for the association.

Forty four articles investigated the association between knee OA and DM; 27 studies of them concluded that there was a significant relationship or at least reported an OR >1 in the text.

Murata et al. [56]; Arellano-Perez et al. [3] & Dubey et al. [46] reported the association between DM and OA by measuring certain substances in the synovial fluid they found elevated expression of TLR4 and MMP13, higher concentrations of cartilage oligomeric matrix protein in synovial fluid (SF COMP) in the synovium of osteoarthritis patients with high hemoglobin Al c (HbAlc) concentrations, Matrix metalloproteinase-1, aggrecan (AGN), type II collagen (Col II), SOX9, and increased carboxymethyl lysine (advanced glycation end product) are all signs of damaged articular cartilage and proteoglycans. Meniscal degeneration was linked to higher fasting glucose and HbAl c levels, according to [44].

According to osteophytes-defined radiographic knee OA prevalence, cardiometabolic dysfunction persists within subgroups distinguished by obesity status and gender [51]. In each BMI category, phenotypes of body size with metabolic abnormalities were more closely associated with knee osteoarthritis than their metabolically healthy counterparts [54].

Sex studies used MRI and showed an increased change in cartilage characteristics articular cartilage T2 values were greater and more heterogeneous, indicating increased articular cartilage degradation and meniscus alteration related to diabetes [25,26,30,32,34,50] in addition to study by Altinel et al. [40] showed quadriceps buckling was more prevalent in diabetic patients.

Handa et al. [50] and Zaharia et al. [64] used radiological assessment and measuring isometric knee extension strength (KES), ROM, and WOMACquestionnaire, they found that OA is one of the related musculoskeletal diseases that is associated with type 2 DM with lower ROM and lower balance skill, in addition, a study by Fatemi et al. [48] reported high prevalence of musculoskeletal manifestations was associated with DM, Knee osteoarthritis is one of this manifestation. Abourazzak et al. [41] conclude that knee OA is one of the articular and abarticular manifestations in diabetic patients .MetS and its components are largely related to worse pain trajectories through central obesity, according to Pan et al. [57] and Xie et al. [60], implying that MetS may cause the development and maintenance of poorer pain trajectories.

Afifi et al. [69] determine the elevated prevalence of Knee OA among diabetes patients, with worse pain, a higher functional impairment score, and more advanced radiographic abnormalities, in addition, a study by Puenpatom& Victor, [57] found that people with OA had greater prevalences of all cardiovascular risk factors than people without OA overall. Diabetes patients were more likely to have knee OA than non-diabetic controls [55].

Yasuda et al. [61] and Lee et al. [53] found that when the number of metabolic syndrome (MetS) components increased, the severity of knee osteoarthritis generally increased. Four studies showed that DM was associated with higher pain severity that increased with more MetS components, unilateral and bilateral distribution. Regional knee pain, which was linked to moderate to severe walking-related knee pain but not localized or diffuse knee pain, and slower walking speed [47,48,52,63].

Table (1): Studies characteristics and overall quality.

Authors and year of publication	Type of study	Research site	N	Age (range or average)	Diagnosis of OA	Diagnosis of diabetes	Overall quality
Engstrom et al., (2009)	Cohort	Sweden	5082	46-68	- First knee arthroplasty or high tibial osteotomy in combination	Fasting plasma glucose z5.6 mmol/L	Good
Yoshimura et al., (2012)	Cohort	Mountainous and coastal areas	1690	63.9 (11.8)	Radiographic	Serum HbAlc level 5.5%	Good
Eymard et al., (2015)	Cohort	18 countries	559	62.2-63.4	Symptomatic and radiographic	Medical history reported by patients	Good
Pan et al., (2020)	Cohort	Australia	1,099	50-80 years	Symptomatic and radiographic	Fasting plasma glucose >5.6 mmol/L)	Good
Onkarappa et al., (2020)	Cohort	India	41	- The average age of Mets-OA patients is 54.3 Non-Mets OA age is 57	Symptomatic and radiographic	Fasting blood sugar > 100 mg/dl	Good
Stiirmer et al., (2001)	Cross-sectional	Germany	809	63±71	Radiographic	By a history or use of antihyperglycemics.	Fair
Konstariet al., (2021)	Cohort	Finland	6,274	30-98	Symptomatic	Elevated plasma fasting glucose (5.6 mmol/L	Good
Ashmeiket al., (2021)	Cross-sectional	USA	20	40-70	Radiographic, MRI	Fasting glucose (FG), hemoglobin Alc (HbAlc)	Fair
Lee et al., (2019)	Cross-sectional	Korea	8,491	50-79	Radiographic	Fasting glucose z 100 mg/dl or undergoing treatment for diabetes;	Good
Franco et al., (2020)	Cross-sectional	Portuguese	416	73.0±5.6	Radiographic	Blood glucose fasting (> 100mg/DL.	Fair
Yoshimura et al., (2011)	Cohort	Japan	1690	65.2 (12.0)	Radiographic	HbAlc level z 5.5%	Good
Han et al., (2013)	Case-control	Korean	2234	40-90 years	Symptomatic	Fasting glucose z100 mg/dl	Good
Golightly et al., (2021)	Cohort	USA	4093	61.0±10.5	Radiographic, symptomatic	By history	Good
Afifi et al., (2018)	Case-control	Egypt	60	MetS group age 52.8±8.0 Control group age 49.8±8.1	Radiographic, symptomatic	Fasting glucose z100 mg/dl or patient using anti-diabetic drugs	Good
Altinel et al., (2007)	Case-control	Turkey	61	>40 years	Radiographic, symptomatic	Oral antidiabetics, and glycated hemoglobin A (HbAlc) levels	Poor
Funck et al., (2019)	Cohort	Europe	384,838	56.8±8.0	Symptomatic	Self-reported diabetes + a hospital diagnosis of type 2 diabetes	Good
Either et al., (2021)	Cross-sectional	United state	2481	45-79 years	Radiographic, symptomatic	Self-reported diagnosis of prior DM	Good
Zheng et al., (2022)	Cohort	China	17,619	58 years on average	Symptomatic	HbAlc 6.5% (48 mmamol), self-reported medical diagnosis, or acknowledged use of medications that lower blood sugar	Good
Liet al., (2016).	Case-control	China	70	50-75 years	Radiographic, symptomatic	A prior diagnosis of diabetes with treatment or a fasting plasma glucose (FPG) of less than 6.1 mmol/L	Good
Zaharia et al., (2021)	Case-control	Germany	66	58.7±10.9	Symptomatic,	Fasting blood glucose and HbAl	Fair
Murata et al., (2019)	Cross-sectional	Tokyo, japan	342	73.9±0.7	Radiographic	HbAlc z6.5 and HbAlc <6.5	Good
Abourazzak et al., (2014)	A cross-sectional	Morocco	116	61±10 years (35-92 years)	Symptomatic	HbAlc levels were >8.0%.	Fair

Table (1): Studies characteristics and overall quality.

Authors and year of publication	Type of study	Research site	N	Age (range or average)	Diagnosis of OA	Diagnosis of diabetes	Overall quality
Arellano Perez Vertu et al., (2019)	Case-control	Northern Mexico	231	>30	Radiographic	FPG ±126 mg/dL and HbAlc $6.5%	Good
Horn et al., (1992)	Case-control	Indiana	73	>40	Radiographic	Random blood glucose, for the diabetic group 219.1t 116.9 non diabetic group 95.6±13.3	Fair
Dubey et al., (2018)	Cross-sectional	Taiwan	1,255,607	30-89	Proteins levels	Fasting blood glucose (FBG)reached an average of 470 mg/dL in diabetic KOA	Good
Inoue et al., (2011)	Case-control	Japan	795	>20 years	Radiographic	HbAlc>5.8%	Poor
Shin, D. (2014)	Cross-sectional	Korea	2363	z50 years	Radiographic	Using medication or having a fasting blood sugar level of 100 mg/dL or higher.	Good
Kendzerska et al., (2018)	Cohort	Ontario, Canada	16362	z55 years	Symptomatic	(1) diabetes that has been diagnosed by a doctor based on at least one hospital stay or at least two outpatient visits within a two-year period; (2) diabetes was self-reported on the survey; or (3) medication usage for diabetes one year prior to the enrollment date.	Good
Pan et al., (2020)	Cohort	Southern Tasmania	435	50 years	MRI scans	Fasting plasma glucose >5.6 mmol/1	Good
Lee et al., (2015)	A cross-sectional	Korea	1,549	50 years	Radiographic	Serum glucose 100 mg/dL.	Fair
Fatemi et al., (2015)	Cross-sectional	Iran	313	30-79	Symptomatic	Diabetes patients must have a fasting blood sugar (FBS) of 126 mg/dL or a 2-hour postprandial plasma blood sugar (GTT) of 200 mg/dL, while prediabetic subjects must have impaired FBS (100-125 mg/dL) or impaired GTTs (2-hour postprandial plasma blood sugar of 140-199 mg/dL).	Good
Neumann et al., (2019)	Cohort	USA	488	63.14±9.09	MRI scans	Self-administered questionnaire	Good
Karvonen-Gutierrez et al., (2012)	Cross-sectional	USA	1,066	z60	Radiographic	Assessment-insulin resistance (HOMA-IR)	Good
Nieves-Plaza et al., (2013)	A cross-sectional	Hispanics from Puerto Rico	202	51.6 (13.1) years	Symptomatic	1) Diabetic symptoms plus a blood glucose level of 200 mg/dL or 2) a fasting blood glucose level of 126 mg/dL or 3) a 2-hour plasma glucose level of 200 mg/dL during an oral glucose tolerance test)	Good
Jungmann et al., (2013)	Cohort	Modern Western	403	45-60 (mean age 52.1±3.9)	MRI	Self-report of diabetes.	Good
Niu et al., (2017)	Cohort	society	991	z40	Radiographic	Fasting glucose level (110 mg/dL	Good
Chanchek et al., (2018)	Cross-sectional	United States	416	63.0±8.9y (45 to 79 years)	MRI	Self-reported type 2 diabetes (DM) managed with either oral medicine or insulin	Fair
Neumann et al., (2018)	Cohort	USA	392	45-79 years	Radiographic	Self-administered questionnaire	Fair
Rogers-Soeder et al., (2020)	Cohort	United States	987	50-79 years	Radiographic	Self-reported diagnosis of DM, use of anti-diabet-is medications in the past 30 days, or a fasting glucose of z 126 mg/dL.	Good
Kuusalo et al., (2021)	Cohort	USA	4796	50-79 years	Radiographic	Self-reported	Good
Alenazi et al., (2020)	Cross-sectional	United States	1790	69 (8.7) years	Symptomatic	Self-reported DM Comorbidity Index	Good

Table (1): Count.

Authors and year of publication	Type of study	Research site	N	Age (range or average)	Diagnosis of OA	Diagnosis of diabetes	Overall quality
Kidwai et al., (2016)	Cross-sectional	Karachi	413	>40	Radiographic Symptomatic	Not mentioned	Fair
Puenpatom& Victor, (2009)	Cross-sectional	United States	7714	z18 years	Radiographic	Fasting blood glucose concentration 110 mg/dL	Good
Handa et al., (2023)	Cohort		101	61.3 years	Radiographic, Symptomatic	Hemoglobin Alc level	Fair
Xie et al., (2017)	A cross-sectional	China	5764	z40 years	Radiographic	Blood sample FPG z 100 mg/dL (5.6 mmol/L) or currently undergone drug	Good
Alenazi et al., (2020)	Cross-sectional	United States	148	45 to 79	Radiographic, Symptomatic	Self-reported	Good
Tootsi et al., (2017)	Case-control	Tartu in Estonia	55	OA = 63±7 control =61±8	Radiographic	Blood samples	Good
Yasuda et al., (2018)	Cross-sectional	Japan	119	45-88 years	Radiographic	Random blood glucose level200 mg/di	Fair
Yerima & Adelowo, (2017)	A cross-sectional	Nigeria	244	18-73 years	Radiographic	Fasting glucose > 5.6 mmol/L.	Fair
Yoshimura et al., (2015)	Cohort	Mountainous and coastal regions	1,690	s3980	Radiographic	Serum HbAlc level 5.5%	Good

Study or Subgroup	knee OA Events	knee OA Total	knee no OA Events	knee no OA Total	Weight	Odds Ratio 1141, Random, 95% CI
MS et al., (2018).	39	50	2	19	7.3%	30.14 [6.02, 150.88]
Arella no Perez Verttiet al.,(2019).	92	121	50	110	15.0%	3.81 [2.17, 6.67]
Franco alai., (2020).	23	76	45	106	14.5%	0.59 [0.32,1.10]
Inoue et al., (2011).	13	251	22	532	13.9%	1.27 [0.63, 2.56]
Nieves-Plaza et al, (2013).	49	76	51	126	14.8%	2.67 [1.48, 4.81]
Puenpatom Vlctor,(2009).	299	975	755	6739	17.3%	3.51 [3.00, 4.10]
Shin, D. (2014).	134	919	165	1444	17.0%	1.32 [1.04,1.69]
Total (95% CI)		**2468**		**9076**	**100.0%**	**2.26 11.28, 4.01]**
Total events	649		1090			

Heterogeneity: Tau'. 0.49; Chl'= 80.30, df= 6 (P . 0.00001); r= 93%
Test for overall effect: Z= 2.80 (P = 0.005)

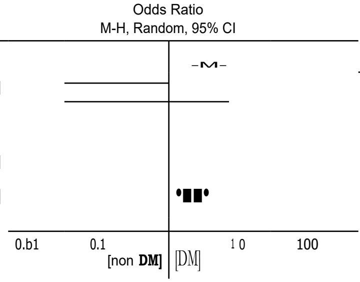

Fig. (3): Risk of diabetes mellitus in knee osteoarthritis.

Shidy or Subgroup	DM Events	DM Total	non DM Events	non DM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ftlenazi et al., (2020).	197	236	1138	1554	5.0%	1.86 [1.29, 2.87]
Chanchek et al.,(2018).	125	208	122	208	5.0%	1.06 [0.72,1.57]
Fatemi et al., (2015).	138	188	48	125	1.6%	4.43 [2.73, 7.191
Kendkerska el al.,. (2018).	399	2128	2431	16362	46.2%	1.32 [1.18, 1.49]
Kidwai et al., (2018).	52	210	54	203	4.2%	0.91 [0.58,1.41]
Kuusalo et al.,(2021).	174	605	2065	7018	23.7%	0.9710.81,1.16]
Neumann et al., (2018).	145	244	145	244	6.0%	1.00 [0.70,1.44]
Neumann et al., (2019).	117	196	117	196	4.8%	1.00 (0.67,1.50]
Rogers-Soeder et al., (2020).	20	94	184	892	2.8%	1.04 [0.62,1.75]
Zaharia et al., (2021)	17	39	10	27	0.7%	1.31 10.48, 3.59]
Total (95% CI)		4148		26829	100.0%	1.24[114,1.351
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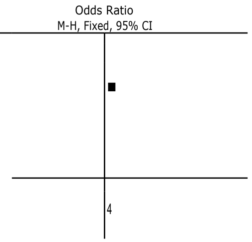

Fig. (2): Risk of knee osteoarthritis in diabetic patients.

Whereas 16 studies displayed no associationbetween knee OA and DM **[23-24,28,29,31,35,39X-44,54, 57, 64,67].** For the meta-analysis, we cannot combine data on the association between DM and knee osteoarthritis because of variations in data presented in studies and diagnostic criteria.

The association between DM and progression of knee OA:

Eighteen studies demonstrated an association between DM and progression of knee OA.The sample size, length of follow-up, diagnostic criteria, and definition of progression varied significantly between investigations.

The sample size ranged from 41 to 384,838 individuals. The duration of follow-up ranged from 6 months to 12 years. At baseline, OA was diagnosed using four separate criteria: Magnetic resonance imaging (MRI), self-reported confirmed by radiography and/or medical records, Kellgren/Lawrence (K/L) grade, and the American College of Rheumatology. Although the studies differed in their definition of progression, five studies characterized OA progression as joint space narrowing (JSN) alone **[25,29,31,36,37].** Two studies classified OA progression as a first knee arthroplasty or high tibial osteotomy along with an OA diagnosis **[21,23],** MRI **[26,30,34],** symptomatic **[27,28,38]** and 5 used a combination of JSN and symptomatic **[22, 24,32,33,35].** For the meta-analysis, no ORs were available for the association between DM and the progression of the knee because of variations in diagnostic and progression criteria.

Meta-analysis:

Risk of knee osteoarthritis in diabetic patients:

Ten studies were used to calculate the risk of knee osteoarthritis in diabetic patients **[25,27, 29,30,35,48,50,53,57,69].** For the risk of OA in DM versus non-DM subjects, among 4148 patients, the overall OR was 1.24 (CI 1.14 to 1.35), with high heterogeneity (I^2=80%) (Fig. 2).

Risk of diabetes mellitus in knee osteoarthritis:

Seven studies were utilized to investigate the risk of DM in OA people vs. non-OA subjects in 2468 patients. Because I^2=93%, a random-effects model was utilized to calculate the overall OR, which was 2.26 (1.28 to 4.01) **[3A0,43,54,60,62, 63].** By eliminating the low-quality papers from our sensitivity analysis, we were able to strengthen the results, but the degree of heterogeneity remained same (Fig. 3).

Discussion

Diabetes millets have been related to OA for years, but their significance to OA remains unclear and conflicting in several studies. This study discovered a direct association between diabetes and structural knee OA deterioration, rather than just chronic joint discomfort. This finding not only supports additional research into the primary risk factor for OA, diabetes, from the tissue to the molecular level, but it also provides a new way of thinking about OA etiology and treatment strategies.

This systematic review and meta-analysis intended to define the association between knee Osteoarthritis and Diabetes Mellitus. This study outcome showed that there is a strong association between diabetes and knee OA in addition the prevalence of diabetes among OA patients and vice versa was calculated, and the results showed that the mean OA prevalence was 34.29% among 4403 diabetic patients, the DM prevalence was 23.45% among 12361 OA patient that means both disease is leading cause for others.

Our findings are consistent with recent systematic reviews **[70,71],** which found minimal evidence to suggest that poor glucose metabolism was a risk factor for OA, even though the current research shows a link between knee OA and diabetes mellitus. This contradicts the findings of two prior meta-analyses on the same subject **[72,73].**

When compared to the two prior meta-analyses, our new findings have several advantages. Our updated literature search found several new and bigger cohort studies that revealed a relationship between DM and knee OA **[25,30],** although two of them showed no association **[29,35].**

Ten studies were used to calculate the risk of knee osteoarthritis in diabetic patients, for the risk of OA in DM versus non-DM subjects, among 4148 patients, the overall OR was 1.24 (CI 1.14 to 1.35), with high heterogeneity (I^2=80%).

The heterogeneity between studies was substantial, most likely due to changes in OA diagnosis criteria, DM definition, and study types and quality. To account for this heterogeneity, we conduct a sensitivity analysis to see if the relationship between OA and DM was maintained after eliminating papers with poor methodology, and we found that it did in all sensitivity analyses.

Seven studies were utilized to investigate the risk of DM in OA people vs non-OA subjects in 2468 patients. Because I^2=93%, a random-effects model was utilised to calculate the overall OR, which was 2.26 (1.28 to 4.01). By eliminating the low-quality papers, we conducted sensitivity analyses to reinforce the results, but the heterogeneity remained unchanged.

There is a different mechanism that may explain this association;may hyperglycemia tends to shift the cartilage homeostasis towards degeneration by increasing in the serum levels of COMP in MetS-OA group compared to non-MetS OA group. However, serum PIIANP levels were comparable in both the groups. This indicates predominant effect

of MetS on increased rate of degeneration without any significant effect on reparative process **[32],** increased meniscal degenerationby higher WORMS meniscus sum **[44],** elevate the expression of Toll-like receptor 4 (TLR4) that was associated with catabolic response via regulation of matrix metalloproteases (MMPs) **[56],** destruction of joint cartilage by an increase in synovial fluid (SF) cartilage oligomeric matrix protein COMP concentrations in T2D subjects. It was observed that the non-KOA/T2D patients had a greater concentration of SF COMP levels. Given that exposure to high glucose environments may cause cartilage matrix breakdown, this may be a sign of early OA in diabetic people without symptoms on the knee joint or severity of OA [3]. Greater knee structural deterioration, stratified by the severity of the diabetes, and greater knee deterioration in diabetics with more severe diabetes, as shown by the use of insulin and the existence of diabetic comorbidities. According to Neuman et al., the overproduction and accumulation of AGEs may be triggered by a hyperglycemic environment, which may alter the hyaline cartilage's tensile properties. This may ultimately increase the cartilage's stiffness and fragility, making it more susceptible to damage and degeneration **[30].**

A vicious cycle that maintains metabolic dysregulation and worsens joint symptoms is created by the fact that diabetes-related increased articular cartilage degeneration promotes cartilage degeneration and joint inflammation, enriching advanced glycation end products and impeding optimal joint cushioning .faster deterioration of the cartilage matrix in the knee of diabetics, indicating a higher loss of collagen content with a disruption of the collagen network in the extracellular matrix with more water influx, in the deeper layers of the cartilage in the diabetics, findings which are different from non-diabetics and also different from the normal evolution of cartilage degenerative disease, which starts at the superficial layer of diabetic knees, possibly causing accelerated OA **[1,25,50].** Obesity showed the closest association with knee osteoarthritis. Abdominal obesity might affect knee OA development by the combined metabolic effects of adipose tissue and mechanical stress of body weight **[54].**

Falsarella et al. **[49]** &Kidwai et al. **[52]** conclude that knee OA is associated with WC, addition Han et al. **[39]** agreed with this opinion and showed that WC was associated with knee OA in female.

The association between diabetes mellitus and knee OA is still debates; we need further research with high-quality studies with defined patient characteristics and with defined diabetic type and duration to decrease heterogeneity to reach a real association. The implication of our study is to control DM and OA and take precautions to avoid progression if one of them is developed and to stop this vicious cycle.

The strength of our study is that it is based on pre a planned study protocol that included a systematic search of EMBASE, MEDLINE / PubMed, Cochrane Library Web search, Scopus, and SAGE, to obtain pertinent studies, the majority of studies were cohort studies presented good quality, We performed sensitivity analyses and excluding the poor quality studies to strengthen the result.

The considerable degree of heterogeneity among the studies was the primary drawback of the current investigation. This might be accounted for by the population's varied features as seen in the numerous research.The random effect models have been used as a result. Despite efforts to reduce this through sensitivity studies in multiple subgroups, there was still a significant amount of variabilitySecond, we draw the conclusion that research using case-control and cross-sectional designs, as well as the vast majority of investigations, failed to specify the type of diabetes mellitus.

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العلاقة بين تطورالالتهاب العظمي المفصلي للركبه وداء السكرى (دراسة منهجيه وتحليل احصائى)

ان الغرض من هذه الدراسه معرفة العلاقه بين تطور الالتهاب العظمى المفصلى للركبه وداء السكرى. تم تحديد ٥٠ دراسه خلال البحث الالكترونى فى ٦ قواعد للبيانات منذ البداية وحتى شهر فبراير ٢٠٢٣ .

كانت ١٨ دراسه حشديه رجعيه فى حين ان ثمانى دراسات بالملاحظة و٢٤ دراسه مستعرضه تم استخدام مقياس نيوكاسل أوتاوا، وهو مقياس لتقييم مخاطر التحيز للدراسات القائمة على الملاحظة التى أقرتها مؤسسة كوكرين، قام باحثان بتقييم جودة المنشورات المختارة بشكل مستقل أغلبية الدراسات كانت من نوعيه جيده . ٣٤ من نوعيه جيده ١٤ من نوعيه معتدله و٢ من نوعيه ضعيفة .

تم استخدام عشر دراسات لحساب مخاطر الإصابة بالتهاب مفصل الركبة فى مرضى السكرى، من بين ٤١٤٨ مريضاً كان معدل الأرجحية الكلى ١,٢٤ فى حين تم استخدام سبع دراسات للتحقيق فى مخاطر الإصابة بمرض السكرى فى الأشخاص المصابين بالتهاب مفصل الركبة مقابل الأشخاص غير المصابين بالتهاب مفصل الركبه فى ٢٤٦٨ مريضاً. وكان معدل الارجحيه ٢,٢٦.

كان التباين بين الدراسات كبيرًا، على الأرجح بسبب التغييرات في معايير تشخيص التهاب مفصل الركبه ، وتشخيص مرض السكرى، وأنواع الدراسة وجودتها. لحساب عدم التجانس هذا، تم اجراء تحليل الحساسية لمعرفة ما إذا كانت العلاقة بين االتهاب مفصل الركبه ومرض السكرى قد تم الحفاظ عليها بعد استبعاد الأوراق ذات المنهجية السيئة، ووجدنا أنها فعلت ذلك فى جميع تحليلات الحساسية.

أظهرت ثمانى عشرة دراسة وجود علاقة بين مرض السكرى وتطور التهاب الركبة. اختلف حجم العينة وطول المتابعة ومعايير التشخيص وتعريف التقدم اختلافًا كبيرًا بين التحقيقات.

كان متوسط انتشار التهاب مفصل الركبه بين مرضى السكرى ٤٣,٢٩٪ بينما كان معدل انتشار مرض السكرى بين مرضى التهاب مفصل الركبه ٢٣,٤٥٪.